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Case Report

Navigating the diagnostic maze: the challenge of sclerosing pneumocytoma in frozen sections

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Abstract: Pulmonary Sclerosing Pneumocytoma (PSP) represents a rare benign tumor that exhibits a predisposition towards females. Often asymptomatic, its identification usually occurs incidentally through imaging modalities. Histologically, PSP demonstrates features consistent with pneumocytic differentiation and possesses a dual-cell population. However, in rare instances it may demonstrate pleural invasion or lymph node metastasis. Diagnosing PSP through small biopsy or frozen section presents considerable challenges attributed to its heterogeneous growth patterns and striking similarity to well-differentiated pulmonary adenocarcinoma. We report a case of PSP in a 57-year-old female smoker, presenting as a slow-growing 2.5 cm mass that recently exhibited enlargement, as noted on computed tomography (CT) scan. The recommendation for excising the mass prompted the patient to undergo a right robotic-assisted thoracoscopic procedure, which entailed wedge resection of the right lower lobe and an intraoperative consultation. A completion right lower lobectomy was performed, accompanied by lymph node dissection, following a frozen section diagnosis indicating at least adenocarcinoma in situ. The permanent section revealed bland cuboidal cells lining papillary and sclerotic areas, with occasional atypical features such as prominent nucleoli and scattered mitotic figures. Adjacent foci of atypical adenomatous hyperplasia (AAH) were noted. Immunohistochemical (IHC) staining revealed positive Napsin A, keratin AE1/3, and CK7 in surface cells but not in round cells. Both EMA and TTF1 immunostains highlighted surface cells and scattered round cells. Elastic stain highlighted visceral pleural involvement. The combined morphology and immunoprofile supported the diagnosis of PSP. This case underscores the critical importance of accurately diagnosing slow-growing pulmonary nodules, which are increasingly detected by the widespread use of imaging for various medical conditions.

Keywords: Pulmonary sclerosing pneumocytoma, imaging, morphology, immunohistochemistry

Introduction

Pulmonary Sclerosing Pneumocytoma (PSP) was first described by Liebow and Hubbell in 1956 [3]. It is an indolent neoplasm believed to originate from primitive respiratory epithelial cells, predominantly type II alveolar pneumocytes, as indicated by immunohistochemical studies [3, 4]. In the 2015 WHO classification for lung and pleural tumors, PSP was reclassified among adenomas/epithelial tumors from the miscellaneous group [5, 6]. The histomorphologic requirement for PSP is the concurrent presence of cuboidal surface epithelial cells and stromal round cells, both of which are considered to be neoplastic in nature and are pathognomonic for this diagnosis [2, 4]. Even though it is considered benign, it can exhibit features such as pleural invasion, as in our case, or lymph node metastasis [7-11] or local recurrence [12]. The increased use of imaging has led to a higher prevalence of benign pulmonary nodules [13]. Since it presents as a slow-growing lesion on imaging studies, it frequently mandates a frozen section, which can be challenging and get misdiagnosed as a well-differentiated pulmonary adenocarcinoma.

Case report

A 57-year-old woman with a history of smoking, coronary artery disease, COPD, kidney stones, and diabetes was referred to our safety net hospital for evaluation. She had a right lower lobe lung nodule persisting for the last 17 years, which recently showed an increase in size on imaging (**Figure 1**). The patient reported symptoms of shortness of breath and fatigue but

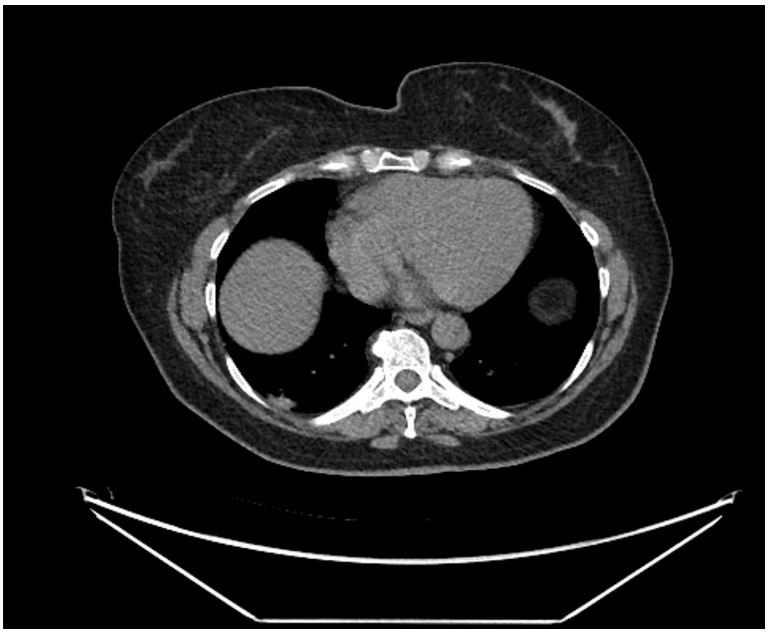

Figure 1. CT scan of the nodule. The CT scan shows a well circumscribed right lower lobe nodule, measuring 2.5 × 1.0 cm.

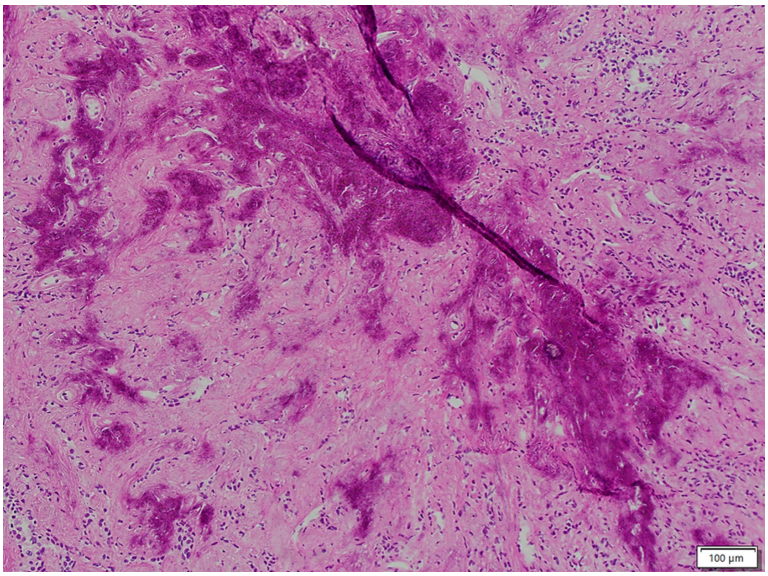

Figure 2. Histologic examination of the frozen section. Histologic examination (10×) reveals the frozen section artifact masking the sclerosed part during intraoperative diagnosis.

denied any history of cough, chest pain, hemoptysis, fever, chills, night sweats, or weight loss.

A subsequent positron emission tomography imaging (PET)-CT scan confirmed the presence of a right lower lobe pulmonary nodule, measuring 2.5 cm in size, previously 1.9 cm. The patient was referred to thoracic surgery, and a wedge resection was performed. The resected specimen was then submitted for an intraoperative frozen section. Sectioning the specimen revealed a firm, tan-white lesion measuring 2.1 × 2.0 × 1.1 cm. The frozen section diagnosis was suggestive of lepidic pattern adenocarcinoma with areas of fibrosis and atypical adenomatous hyperplasia in the background (**Figure 2**). This resulted in completion lobectomy, and mediastinal lymph node dissection was performed. All were submitted as permanent specimens.

Histologic examination of the lesion revealed papillary, solid, and fibrotic areas lined by bland cuboidal cells on the surface, with round cells present in the stroma (**Figure 3A**, **3B**). A few cells showed mild cytologic atypia with occasional small but conspicuous nucleoli and rare mitotic figures. Visceral pleural invasion was identified and confirmed by elastic stain (**Figure 4**). Foci of atypical adenomatous hyperplasia (AAH) were identified in the background, which raised the possibility of lepidic pattern adenocarcinoma on frozen section (**Figure 5**).

Discussion

PSP, previously called pulmonary sclerosing hemangioma, is a rare benign neoplasm that typically presents in the 5th decade, with a female predilection. It is often discovered incidentally during routine chest imaging as a well-circumscribed, unilateral mass [1, 3]. While most patients remain asymptomatic, a small percentage may experience symptoms such as hemoptysis, dyspnea, chest pain, or cough [1, 14]. CT scans reveal a solid, peripheral lesion measuring 2-3 cm in size, characterized by smooth margins

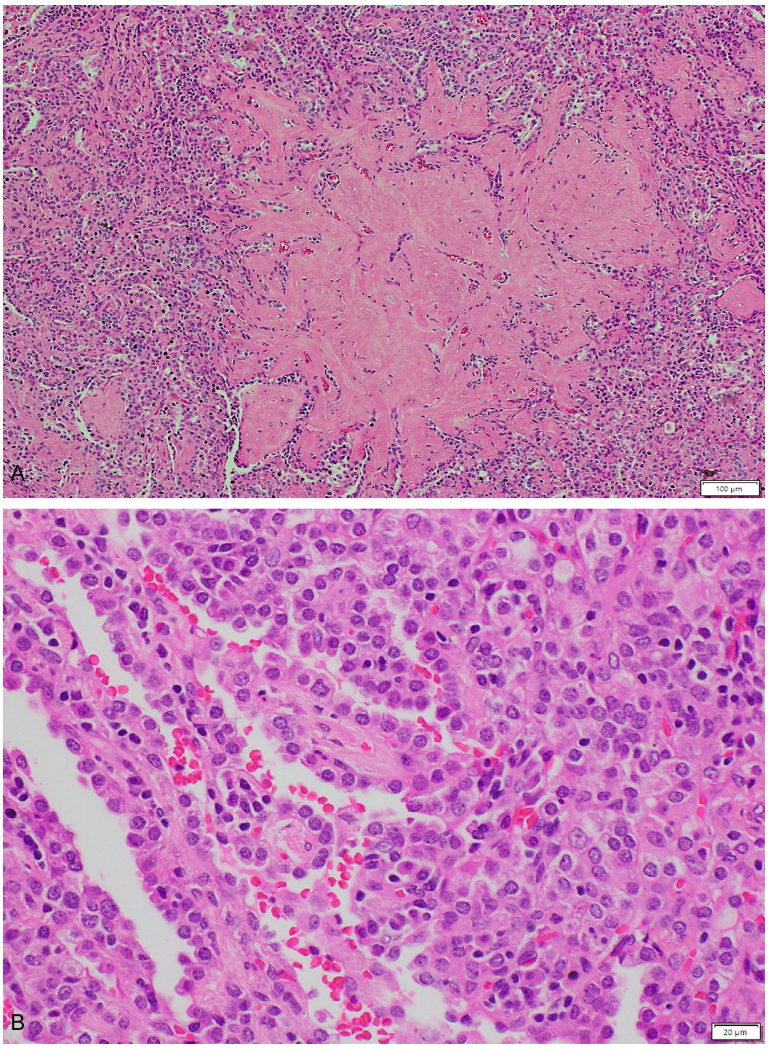

Figure 3. Histologic examination of the nodule. A: Low power view (10×) shows a central fibrotic area surrounded by epithelial proliferation with papillary architecture, consistent with sclerosing pneumocytoma. B: High-power view (40×) depicting two cell populations. Cuboidal cells line the periphery of papillae, and the stromal cells populate the cores.

and occasional calcifications. In some cases, CT-scan may show "air meniscus sign" which is a crescentic radiolucency around the lung nodule, due to air-trapping or hemorrhage around the lesion [2, 3, 21]. There is no specific or diagnostic characteristic of PSP and the air meniscal sign can be seen in entities including carcinoid, aspergilloma, hamartoma, or hemangioma [20, 22]. PSP tumors exhibit PET avidity. On macroscopic examination, they commonly present as well-defined, solid, firm tan subpleural masses ranging from 0.3 to 7 cm in size, with focal areas of hemorrhage. These masses are frequently located in the periphery of the lung or along a fissure. They rarely present as endobronchial polypoidal masses [23].

Histopathologic examination reveals two distinct types of epithelial cells: surface cuboidal cells and round polygonal stromal cells, organized in four distinct architectural patterns - papillary, sclerotic, solid, and hemorrhagic. The bland surface cuboidal cells lining the surface of the papillae exhibit abundant lamellar bodies, since they are derived from Type II pneumocytes and are called the lining cells. The round stromal cells, located in the interstitium, may be oval or polygonal with clear cytoplasm and fine chromatin. Both cell types exhibit positive immunoreactivity for cytokeratin AE1/AE3, EMA, and TTF1 [1, 15]. The surface cuboidal cells also express Napsin A, while the round stromal cells display immunoreactivity for CK7 and CAM5.2 [1, 19]. Necrosis, significant cytologic atypia, or increased mitotic activity are not commonly seen.

Our case revealed sheets of bland-appearing cuboidal cells lining the papillary and sclerotic areas, with oval, bland cells within the stroma. A few cells showed mild cytologic atypia with occasional small but conspicuous nucleoli and rare mitotic figures, in addition to visceral pleural invasion. Foci of atypical adenomatous hyperplasia, which were observed on the frozen section slides, were confirmed in permanent sections as well (**Figure 5**). This was a diagnostic pitfall, as it also suggested the diagnosis of lepidic pattern adenocarcinoma on frozen section. Areas of fibrosis within the lesion were noted, but hemorrhagic foci were inconspicuous.

Immunohistochemical stains were performed on paraffin sections of the right lower lobe using antibodies directed against the following

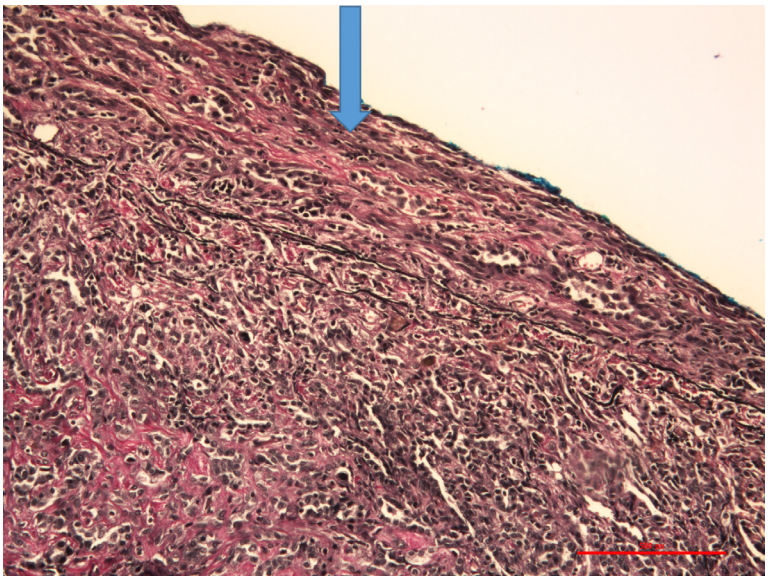

Figure 4. Elastic stain. The elastic stain confirms the visceral pleural involvement (arrow) (10×).

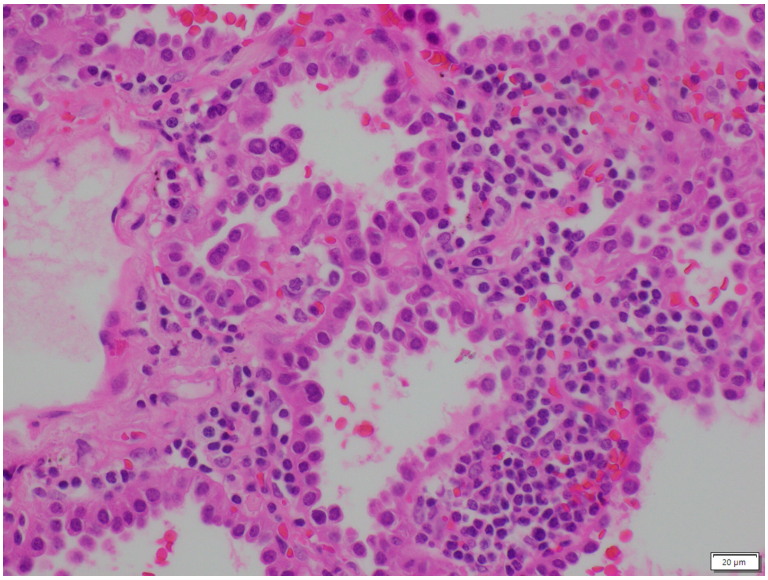

Figure 5. Atypical adenomatous hyperplasia (AAH). Foci of atypical adenomatous hyperplasia are identified in the background lung parenchyma (40×).

antigens: TTF1 (clone SPT24), CK7, EMA, Napsin A, and estrogen receptor. TTF1 highlighted both the round cell and surface lining cells (**Figure 6A**), while estrogen receptor was weakly expressed in the round cell component. The surface lining cells were also positive for Napsin A, cytokeratin AE1/AE3, and CK7 (**Figure 6B**). EMA immunostain highlighted the surface cells and scattered round cells (**Figure 6C**). Elastic stain revealed visceral pleural invasion by the tumor (**Figure 4**). This immunoprofile, along with the morphology, supported the diagnosis of PSP.

The background lung parenchyma showed chronic bronchiolitis and foci of atypical adenomatous hyperplasia, which posed a pitfall on the limited frozen section material, as it favored the main lesion to be a well-differentiated adenocarcinoma. These foci of AAH may represent the small sub-centimeter nodules observed in the CT scan.

Immunohistochemical stains are particularly useful in diagnosing pulmonary sclerosing pneumocytoma (PSP), especially for differentiating it from well-differentiated adenocarcinoma.

PSP can be challenging, especially on small biopsy or frozen section, where it may be mistaken for an adenocarcinoma, particularly if a papillary pattern predominates [18]. This diagnostic challenge is further compounded by freezing artifacts that introduce complexity, possibly causing pathologists to overlook the distinctive sclerosing component of PSP, as in our case.

When evaluating an imaging finding of a lung lesion with the morphologic heterogeneity of a PSP, other differential diagnoses to be considered should include well-differentiated adenocarcinoma, including the lepidic and papillary patterns, metastatic carcinoma with papillary architecture (such as thyroid carcinoma and papillary renal cell carcinoma), and carcinoid tumor [14].

Due to the presence of distinct papillary architecture, PSP is frequently mistaken for adenocarcinoma with papillary features, such as

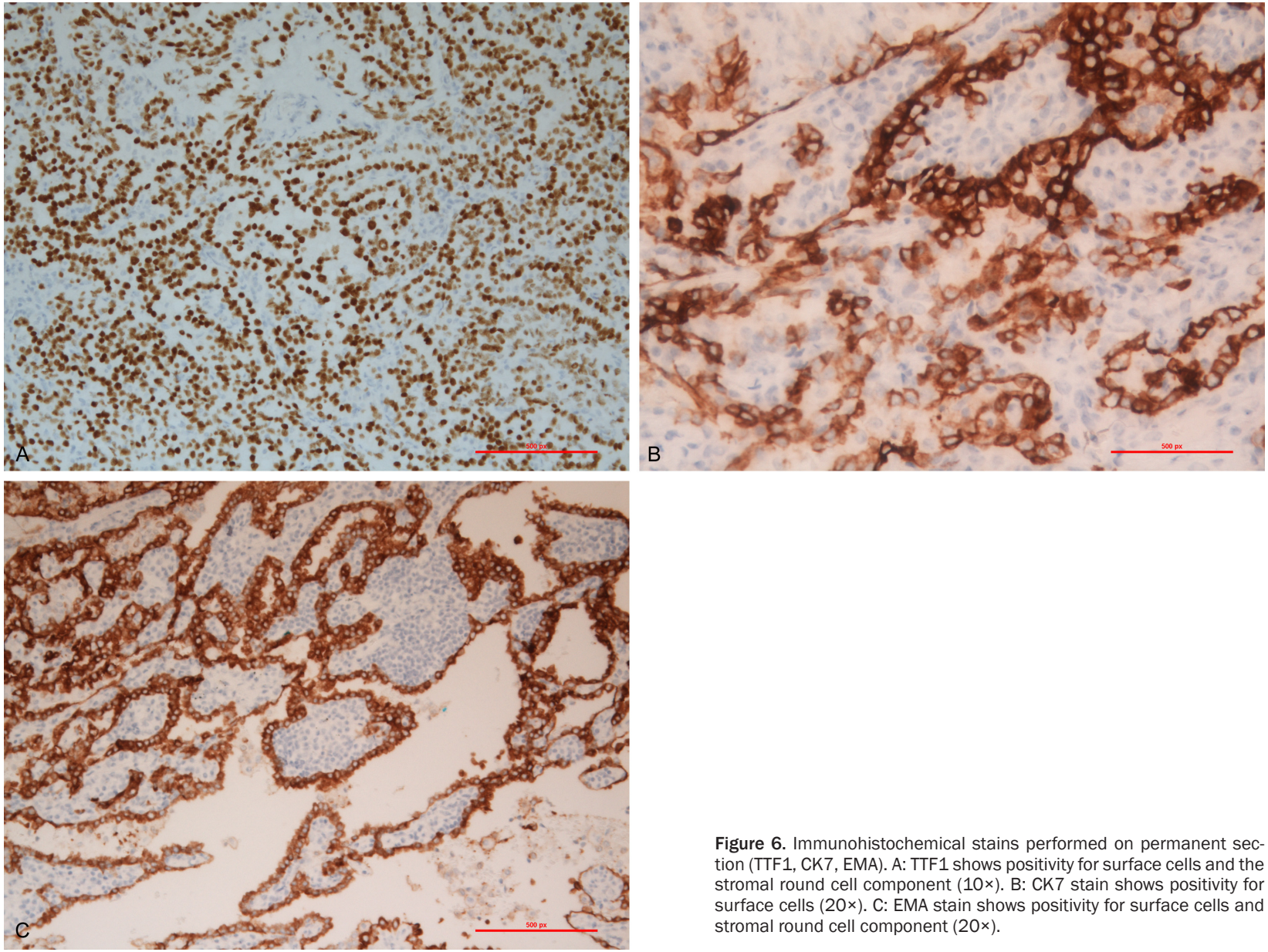

Figure 6. Immunohistochemical stains performed on permanent section (TTF1, CK7, EMA). A: TTF1 shows positivity for surface cells and the stromal round cell component (10×). B: CK7 stain shows positivity for surface cells (20×). C: EMA stain shows positivity for surface cells and stromal round cell component (20×).

those of pulmonary origin and metastatic papillary thyroid carcinoma. Papillary adenocarcinoma lacks the biphasic morphology of PSP (surface cuboidal and stromal round cells) and consists of only one cell type. Moreover, bland cytology and a combination of architectural patterns such as solid, sclerotic, and hemorrhagic pools should raise the possibility of PSP. Other findings that suggest adenocarcinoma over PSP include the presence of mitosis, cytologic atypia such as nuclear membrane irregularity, conspicuous nucleoli, and nuclear overlapping. Immunohistochemical (IHC) stains will show positivity for TTF1 in both cases, but in adenocarcinoma, it is more diffuse across all cell types.

Metastatic papillary thyroid carcinoma (PTC) is included in the differential diagnosis due to its architectural similarity and low-grade cytology. However, the characteristic cytologic features of PTC, such as chromatin clearing, intranuclear cytoplasmic pseudoinclusions, and nuclear grooves, are lacking in PSP. Immunohistochemical stains for TTF1 are positive in both PSP and PTC, but thyroglobulin and PAX8 will be positive only in PTC. Additionally, a history of thyroid carcinoma may be present, emphasizing the importance of accurate clinical history.

Papillary renal cell carcinoma can also be included in the differential diagnostic list of PSP due to its morphologic overlap. However, cytology and immunoprofile are different. Papillary renal carcinoma will have one cell population, although type 2 may have high-grade cytologic features. AMACR, CD10, and PAX8 will be positive, while TTF1 will be negative.

Carcinoid tumors also present as well-circumscribed lesions, more frequently endobronchial. They are low-grade lesions composed of uniform polygonal cells, with round to oval nuclei exhibiting salt-and-pepper chromatin, inconspicuous nucleoli, and moderate to abundant eosinophilic cytoplasm. Spindle cells and clear cell features can be observed. The cells are typically arranged in organoid/nested, trabecular, or rosette formations, although pseudoglandular and papillary patterns can also be seen. Like PSP, they are cytologically bland, lack significant mitotic activity and necrosis. However, immunohistochemical stains, with expression of neuroendocrine markers (CD56, INSM-1, synaptophysin, and chromogranin), will confirm the diagnosis.

Surgical resection is the established approach for treating PSP, demonstrating a favorable prognosis [7, 16]. In specific situations where surgical intervention is not feasible due to the patient's condition, radiotherapy may be considered as an alternative [17]. Rare cases of lymph node metastasis have been demonstrated [23, 24].

Our patient underwent wedge resection with completion lobectomy and lymph node dissection, revealing no signs of metastasis. Subsequent follow-up examinations demonstrated enhanced respiratory function post-surgical intervention, with no complications or indications of recurrence according to the latest imaging results.

Conclusion

Our case aligns well with the diagnostic criteria for sclerosing pneumocytoma, emphasizing the need to recognize this challenging condition. Especially during intraoperative consultation, it can easily be mistaken for lung adenocarcinoma, particularly if pleural invasion is present. The key takeaway is the importance of careful consideration, assessment, and differential diagnosis during intraoperative assessment to accurately guide the clinical team in managing the patient's care.

Navigating the complexities of pulmonary neoplasm diagnoses, our study highlights the effectiveness of ancillary testing combined with morphology in accurately diagnosing this benign entity. The crucial roles of both clinicians and pathologists in being vigilant about this condition should ensure accurate identification, and timely interventions for better outcome.

Disclosure of conflict of interest

None.

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